REMARKS

Reconsideration is requested.

Claims 24 and 25 have been amended above. Support for the recited range of the amended claims may be found, for example, in the specification at page 12, line 25 and in Figure 3, which describes SEQ ID NO:147.

The specification has been amended to include the attached new Sequence Listing. The Sequence Listing has been corrected in SEQ ID NO:147 in nucleotide 50 to include the "S" of figure 3, sequence BE98, which also corrected SEQ ID NO:148 of the Sequence Listing, as disclosed in Figure 5 of the application. The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added.

The format of claim 24 is similar to allowed claim 1 of the related U.S. Patent No. 6,762,024, which contains the same disclosure as the present application, and was issued by the present Examiner. Claim 1 of the related U.S. Patent No. 6,762,024, provides as follows:

> "1. An isolated polynucleic acid sequence consisting of 8 or more contiguous nucleotides selected from:
> an HCV type 3a genomic sequence selected from the region spanning positions 417 to 957 of the Core/E1 region of HCV subtype 3a, wherein said polynucleic acid sequence is capable of hybridizing to HCV subtype 3a, but not another subtype of HCV;
> the complement of said polynucleic acid,
> wherein said polynucleic acid contains at least one genotype 3a-specific nucleotide."

The related U.S. Patent No. 6,762,024, is listed on the attached PTO 1449 Form to insure consideration of the same by the Examiner. Return of an initialed copy of the attached PTO 1449 Form, pursuant to MPEP § 609 is requested.

The claims of the related U.S. Patent No. 6,762,024 provide subtype 3a genomic sequences. The claims of the present application provide subtype 3c genomic sequences. The present specification, which is the same as the specification of the related U.S. Patent No. 6,762,024, describes and is enabling for the claimed subtype 3c sequences of the present application in the same manner that the present Examiner confirmed that the specification adequately describes and enables subtype 3a sequences of the related U.S. Patent No. 6,762,024.

The claims refer to the segment spanning positions 1 to 346, as exemplified by SEQ ID NO:147. The specification is believed to provide an adequate written description of the claimed invention.

Withdrawal of the Section 112, first paragraph "written description", rejection of claims 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54 and 56 is requested.

The Section 112, first paragraph "enablement", rejection of claims 24-57 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Initially, the applicants request clarification with regard to the following remark from the Examiner in the event this rejection is maintained after entry and consideration of the present Amendment:

> "The instant application does not teach one of skill in the art how to make and use oligonucleotide probes or primers with the claimed properties of specificity of hybridization resulting

> from the sequences that the various HCV types and subtypes have in common as is evidences by the Figures in the application." See, page 3 of the Office Action dated May 18, 2005 (emphasis added).

The Examiner is urged to appreciate that each of the claimed probes or primers requires at least 1 genotype-specific nucleotide. The properties of the claimed probes and primers are not the result of common structure of the disclosed genotypes and subtypes, as suggested by the Examiner. It is believed to be well known in the art, even in the art of HCV, that distinguishing HCV genotypes in fact is a variation on the theme of detecting/distinguishing single nucleotide polymorphisms. In fact, the applicants assignee has developed and commercialized an HCV genotyping kit based on this principle and exploiting the even more conserved 5'untranslated region of the HCV genome, see, e.g., US patent No. 5,846,704 (of record). One skilled in the art would know how to make or use the claimed oligonucleotide primers or probes.

The Examiner's reliance on the newly cited Kennell (Progr. Nucl. Acid Res. Mol. Biol. 11: 259-301 (1971)) suggests that the Examiner believes that an upper limit of, for example, 50 nucleotides, should be included in the claimed fragment. See, page 3 of the Office Action dated May 18, 2005. The Examiner is requested to advise the applicants in the event this is not a correct interpretation of the Examiner's remarks and/or intention. To the extent the applicants understand the Examiner's stated reliance on Kennell, the applicants submit that the teaching of Kennell is only instructive with regard to Kennell's fragment and would not be understood by one of ordinary skill in the art, at the time of the present invention, to be generally applicable to the presently claimed invention.

Specifically, for example, Kennell would be understood by one of ordinary skill in the art to only apply to perfectly matching hybrids. Kennell states on page 261, lines 10-11 that

> "The thermal **stability** of a nucleic acid duplex is **extremely sensitive to the presence of mismatched nucleotide pairs**..." (Bold emphasis added.)

Thus, when variation in a nucleotide at the same position in the genome of different HCV genotypes or subtypes is expected (i.e., as claimed), the size of the oligonucleotide can be increased without loss in discriminatory power. Thus, the stability of the perfectly matching (HCV type 3c-specific) primer/probe with a length of over 50 contiguous nucleotides might not increase relative to shorter primers/probes but the stability of the mismatching (not HCV type 3c-specific) primer/probe of the same length will always be lower. Hence, the inclusion of an upper limit is not believed to be necessary in the broader recitation of the claimed invention.

In addition, an ordinarily skilled person would design HCV type 3c-specific primers/probes to include at least 1 HCV type 3c-specific nucleotide, i.e. design these around, for example, the codons encoding HCV type 3c-specific amino acids. Specifically, for example, one of ordinary skill will appreciate from the present disclosure to design around at least one of Q43, S60 and R67 (see sequence alignment in Figure 5). Other HCV type 3c-specific nucleotides not affecting the encoded amino acid may easily be identified through alignment of HCV sequences of different genotypes (e.g., adenine at position 21 and guanine at position 53 in the first 100 nucleotides of SEQ ID NO:147; see Figure 4). A sufficient amount of direction and guidance is therefore

presented in the present application and withdrawal of the "enablement" rejection of claims 24-57 is requested.

With regard to the Examiner's reliance on Wallace et al. (Methods Enzymol. 152: 432 (1987)) (see, page 3 of the Office Action of May 18, 2005), the Examiner is urged to appreciate that the fragment of Wallace et al. quoted does not exclude the possibility that probes shorter than 14 bases can be found suitable for specific hybridization. See, the wording "tendency" and "probably" in said fragment.

The present Examiner similarly relied on Wallace during the prosecution of the related U.S. Patent No. 6,762,024. The rejection in the related U.S. Patent No. 6,762,024 was withdrawn after making similar arguments as well as citation of Majzoub et al (1983) JBC 258, 14061-14065), which exemplifies successful use of 8-mer primers, and Chan et al (PNAS 76, 5036-5040 (1979)) Copies of these documents are attached and listed on the attached PTO 1449 Form.

The Examiner has further asserted that

> "the instant application does not teach one of skill in the art how to amplify specific DNA sequences using only one primer (Claims 50-57)." See, page 3 of the Office Action dated May 18, 2005.

While the Examiner's comment may reflect the requirements for classical PCR (i.e., exponential amplification), applications resulting in linear amplification usually require only 1 primer. Examples of such applications include "classical" sequencing wherein each of the analyzed strands is amplified separately by a single primer, and linear amplification followed by exponential amplification, such as is taught by Meyerhans et al (Nucleic Acid Research (1992) 20, 521-523 (copy attached and listed on the attached PTO 1449 Form). Amplification

with a single primer is therefore submitted to have been known to those of ordinary skill in the art at the time of the present application.

The claims are submitted to be supported by an enabling disclosure. Withdrawal of the Section 112, first paragraph "enablement", rejection of claims 24-57 is requested.

For completeness, the applicants request further clarification of the Examiner's statement that "There is no prior art of record." On page 5 of the Office Action dated May 18, 2005. Both the applicants and the Examiner have cited art and made the same of record.

Moreover, the applicants submit that in view of the art (e.g., U.S. Patent No. 5,846,704 and other documents discussed above and of record) and in view of the contents of and guidance in the disclosure of the application (see discussion above)

(i) an ordinarily skilled person would be able to make and use the claimed oligonucleotides even if shorter than 14 nucleotides or longer than 50 nucleotides;

(ii) sufficient guidance is provided in the application for the ordinarily skilled person to identify HCV type 3c-specific nucleotides of which there must be at least 1 present in the claimed oligonucleotide;

(iii) in view of (i) and (ii) only a limited number of working examples are believed to be required, if at all, to exemplify the claimed invention;

(iv) the state of the art is believed to have developed to what is taught to every molecular biology graduate student (see, Kennell – published in 1971, Majzoub et al. - published in 1983, Chan et al. – published in 1979, Wallace et al. – published in 1987); especially the principles of hybridization and factors influencing it are mainstream knowledge;

(v) in view of (i) and especially in view of (ii) the alleged "unpredictability of the art" stated on page 5 of the Office Action dated May 18, 2005, is submitted, with due respect, to be overstated;

(vi) in view of (i) and especially in view of (ii), there is not believed to be an astronomical number of possible oligonucleotides within the scope of the claims, as stated on page 5 of the Office Action dated May 18, 2005.

Withdrawal of the Section 112, first paragraph "enablement", rejection of claims 24-57 is requested.

The Section 112, first paragraph "written description", rejection of claims 24-57 stated on pages 5-6of the Office Action dated May 18, 2005, is traversed. Withdrawal of the rejection is requested. The only additional stated basis for the rejection, besides the Examiner's comments relating to the "enablement" rejection (i.e., "the rejection immediately above") is understood to be the Examiner's assertion that

> "The instant application does not adequately describe in writing the myriad oligonucleotides that may possibly meet the criteria of the claims." See, page 6 of the Office Action dated May 18, 2005.

While the courts have explained that "written description" and "enablement" are two separate requirements of Section 112, first paragraph, the Examiner appears to rely, in part, on arguments the Examiner made in support of the later to also apparently support the former. To the extent the Examiner (and/or the Board. In any future Appeal) believes this is appropriate, the applicants also rely on their above arguments in response to the "enablement" rejection to support their request for withdrawal of the "written description" rejection.

As for the Examiner's assertion that the whole of the specification does not "describe in writing" the claimed invention, the applicants respectfully disagree and, for example, submit that the presently claimed invention relating to genotype 3c sequences is described in the present specification in a manner similar to the description of claims to genotype 3a sequences granted by the present Examiner in the related U.S. Patent No. 6,762,024. Withdrawal of the Section 112, first paragraph "written description", rejection of claims 24-57 is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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